IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	**MDL No. 2606** Master Case No. 15-2606 (RBK/JS) Hon. Robert B. Kugler, U.S.D.J. Hon. Joel Schneider, U.S.M.J.
THIS DOCUMENT RELATES TO ALL CASES	

DEFENDANTS' REPLY BRIEF IN RESPONSE TO PLAINTIFFS' OPPOSITION AND IN FURTHER SUPPORT OF DEFENDANTS' MOTION TO EXCLUDE THE TESTIMONY OF PLAINTIFFS' EXPERTS DR. DANIEL LEFFLER AND DR. BENJAMIN LEBWOHL

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I. DRS. LEFFLER AND LEBWOHL'S METHODOLOGY IS UNRELIABLE.

Arguing that Drs. Leffler and Lebwohl employed the Bradford-Hill criteria in analyzing general causation (Dkt. 1109 at 1; Dkt. 1115 at 2) is not enough; these experts must employ those criteria *reliably*. "The expert's assurances that he has utilized generally accepted scientific methodology is insufficient." *Moore v. Ashland Chem. Inc.*, 151 F.3d 269, 276 (5th Cir. 2009).

Here, Drs. Leffler and Lebwohl fail completely to satisfy the reliable application requirement, shoehorning unreliable science into the Bradford-Hill criteria and declaring that enough to establish general causation. That is not the "good grounds" required for admissible expert opinion. *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 590 (1993). "Though courts have afforded experts a wide latitude in picking and choosing the sources on which to base opinions, Rule 703 nonetheless requires courts to examine the reliability of those sources." *Viterbo v. Dow Chem. Co.*, 826 F.2d 420, 422 (5th Cir. 1987) (quoting *Soden v. Freightliner Corp.*, 714 F.2d 498, 505 (5th Cir. 1983)). When assessed through this lens, Drs. Leffler and Lebwohl's Bradford-Hill analyses are revealed as unreliable:

- **CONSISTENCY.** Dr. Lebwohl testified that "a clinical phenotype that's frequently observed" is "an important piece of the consistency criteria in Bradford-

Hill." Dkt. 1109 at 10 (quoting Lebwohl Dep. at 241:6-16). If such a clinical phenotype for "olmesartan enteropathy" exists, Drs. Leffler and Lebwohl have not presented it in this litigation. Instead of defining the phenotype, plaintiffs reinforce the absence of one and hope the Court doesn't notice.

Dr. Lebwohl believes "'[t]here is not a single invariable presentation for this condition,'" and plaintiffs claim that this opinion is "consistent with . . . the literature." Dkt. 1109 at 10 (quoting Lebwohl report). Similarly, plaintiffs concede that Dr. Leffler's definition of "olmesartan enteropathy" is little more than a collection of "the signs and symptoms . . . reported in the peer-reviewed literature." Dkt. 1115 at 7-8. Contrary to plaintiffs' contention (Dkt. 1115 at 6), Dr. Leffler cannot identify "the common symptoms of olmesartan enteropathy." As Dr. Leffler testified, "You know, I don't know that we actually have a full enough understanding of the spectrum of the condition to know what are the most common." Certification of Daniel B. Carroll, Esq. in Support of Leffler and Lebwohl Reply ("Carroll Cert."), Ex. CC, Leffler Dep. at 71:19-22. Dr. Lebwohl concurred: "There's no one uniform set of strict criteria that's been developed" to define "olmesartan enteropathy." Dkt. 1066-1 at 6 (quoting Lebwohl Dep.).

And that's a crucial point: science has not defined a clinical phenotype, and plaintiffs have not identified any literature endorsing the open-ended and variable definition of "olmesartan enteropathy" that Drs. Leffler and Lebwohl endorse.

Instead, Drs. Leffler and Lebwohl cobble together symptoms *associated* with olmesartan in case reports and case series, and declare them part of a unified syndrome called "olmesartan enteropathy." *See* Dkt. 1066-1 at 4-9. These are not reliable sources for a causation opinion. *See* Section II *infra*; Dkt. 1066-1 at 34-40. And Drs. Leffler and Lebwohl's undisciplined grab bag for diagnosing "olmesartan enteropathy" will inevitably generate inconsistent and non-reproducible evaluations of causation evidence, rendering their opinion on what constitutes "olmesartan enteropathy" ill-fit for airing to a jury.

- **STRENGTH.** Drs. Leffler and Lebwohl's review of available epidemiology concerning olmesartan was neither complete nor expert (Dkt. 1115 at 19-28; Dkt. 1109 at 6-8, 12-15). Setting aside the impropriety of Drs. Leffler and Lebwohl's (a) relegation of the weight of existing epidemiology, (b) reliance on non-statistical "trends" in the Lagana study while rejecting that study's statistical findings, and (c) rejection of ROADMAP's statistical conclusions while embracing data serving as the basis for those conclusions (Dkt. 1066-1 at 15-25), their election to omit one of only five available epidemiological studies typifies these experts' aim "to 'pick and chose' [sic] from the scientific landscape and present the Court with what he believes the final picture looks like. This is hardly scientific." *See, e.g., Lust v. Merrell Dow Pharms.*, 89 F.3d 594, 596 (9th Cir. 1996).

Padwal et al. studied 45,185 ARB patients, 10,370 of whom were taking olmesartan, and found no increased risk of gastrointestinal disease-related hospitalization posed by olmesartan. *See* Dkt. 1066-1 at 22-23 (discussing the Padwal study). Conveniently, both Drs. Leffler and Lebwohl bypass this study. *See generally* Cert. in Support of Motion to Exclude Drs. Leffler and Lebwohl ("Leffler and Lebwohl Cert."), Exhibit B, Leffler Rep.; Exhibit E, Lebwohl Rep.

Dr. Lebwohl's subconscious reference to the Padwal study in crafting his opinions, becoming apparent only after he saw the study cited in defense experts' reports (Dkt. 1109 at 14-15), is not the sort of expert assessment of available data envisioned in *Daubert*. *See Scheierman v. San Luis & Rio Grande R.R.*, No. CIV.A. 05Z0036ZLWPAC, 2006 WL 5207239, at *2 (D. Colo. Feb. 10, 2006) ("[T]he expert report is intended to be the culmination of the expert's research, not a beginning point from which the expert works backward, finding the materials to support the conclusions"), Carroll Cert. Exhibit DD.

And if Dr. Leffler believes the Padwal study is limited in some way (Dkt. 1115 at 26), sweeping it under the rug is not the manner in which expert opinion deals with such a limitation. *E.g., JMJ Enters., Inc. v. Via Veneto Italian Ice, Inc.*, No. CIV. A. 97-CV-0652, 1998 WL 175888, at *6 (E.D. Pa. Apr. 15, 1998), *aff'd*, 178 F.3d 1279 (3d Cir. 1999) ("expert testimony that ignores existing data and is based on speculation is inadmissible"), Carroll Cert. Exhibit EE. In any event, the

purported weakness in the study – the length of follow up of study participants – should be of no moment for this expert: Dr. Leffler believes "olmesartan enteropathy" can occur at any time after the first pill (Carroll Cert. Exhibit CC, Leffler Dep. at 50:18-52:7), and the median duration of follow up in the Padwal study (2.3 years) was longer than the timeframe that plaintiffs tout as relevant to Dr. Leffler's opinion that a "cumulative dose effect" presents olmesartan users with "an increased risk" over time (2 years). *See* Dkt. 1115 at 28-30 (discussing "cumulative dose effect" opinion). Whatever may have been the power of this study, it produced results that make it clear that in the U.S. population studied at a 95% confidence level the hazard ratio for developing non-infectious gastroenteritis while taking olmesartan did not exceed 1.69.

Dr. Lebwohl's unrecorded and subconscious reference to the Padwal study and Dr. Leffler's internally inconsistent rejection of the Padwal study data (after having omitted it from his report) are demonstrative of their ends-driven analysis of the available epidemiology. Their assessments of the epidemiological literature do not comport with the requirement that experts must "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999).

- **DOSE RESPONSE.** Drs. Leffler and Lebwohl admit that there is no evidence of a dose response to olmesartan. Dkt. 1066-1 at 25 (quoting Leffler

Dep. and Lebwohl Dep.). Instead of acknowledging the absence of scientific support satisfying this Bradford-Hill criterion, Drs. Leffler and Lebwohl create entirely new criteria in its place: "cumulative dose effect" and "second environmental trigger." *See* Dkt. 1109 at 15; Dkt. 1115 at 28-29. Reliable application of the Bradford-Hill methodology does not include replacing an inconvenient criterion when it does not support the expert's desired conclusion. *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004) (excluding expert who "violated his own standard of proper methodology").

Plaintiffs attempt to support this sleight of hand by rewriting the Bradford-Hill criteria altogether, proclaiming incredibly that "dose-response is not, as Defendants claim, an 'essential' feature of the Bradford-Hill method." Dkt. 1115 at 29. This denial has no foothold in reality: dose response is, in fact, one of the nine enumerated Bradford-Hill criteria. *See, e.g., In re Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, No. CIV.A. 08-08, 2013 WL 1558690, at *3 (D.N.J. Apr. 10, 2013) (stating the nine Bradford-Hill criteria), Certification in Support of Opposition to Motion to Exclude Dr. Wilson, Exhibit D. The Reference Guide on Epidemiology and certain court opinions may not require a dose response to prove general causation (Dkt. 1115 at 29-30), but those sources do not provide the methodology that Drs. Leffler and Lebwohl claim to have employed.

Further, contrary to plaintiffs' assertion (Dkt. 1109 at 15; Dkt. 1115 at 28-

30), the science does not substantiate a "cumulative dose effect" or "second hit" effect. Indeed, neither Dr. Leffler nor Dr. Lebwohl posits those effects as anything more than theoretical. *See* Carroll Cert. Exhibit CC, Leffler Dep. at 52:12-54:1 (speculating on the cause of variation of temporal onset of symptoms); Carroll Cert. Exhibit FF, Lebwohl Dep. at 67:2-14 ("there does appear to require either some sort of cumulative effect of damage or some sort of priming of the immune system or some cofactor . . . as yet unidentified"). Though the Basson study may have observed an increased risk of a drug effect after two years (Dkt. 1109 at 15; Dkt. 1115 at 28), that "support" for Drs. Leffler and Lebwohl's opinion is inapposite: neither Dr. Leffler nor Dr. Lebwohl define a timeframe in light of the wide variance of reported onset of symptoms in the medical literature. *See* Dkt. 1109 at 10-11 (quoting Dr. Lebwohl, "olmesartan enteropathy" appears "generally with an onset in the range of months or (more often) years"); Dkt. 1115 at 15-16 (defending Dr. Leffler's view that a timeframe for risk of "olmesartan enteropathy" cannot be defined).

Moreover, the medical literature to which plaintiffs cite for support of a "second hit" theory does not relate to olmesartan, or are unreliable case reports (*see* Dkt. 1066-1 at 34-40; *infra* at Section II) that do nothing more than report an association particular to two olmesartan patients. *See* Dkt. 1115 at 29 n.15 (referencing three studies: one relating to lupus erythematosus, one relating to

celiac disease, and one report of two cases concerning olmesartan).

This proceeding "must function in the present assessing evidence that presently exists." *In re Propulsid Prods. Liab. Litig.*, 261 F. Supp. 2d 603, 615 (E.D. La. 2003). Even if the Court were to overlook Drs. Leffler and Lebwohl's departure from the Bradford-Hill criteria, their hypothetical "cumulative dose effect" and "second hit" theories are only that: unproven possibilities best left for substantiation in the natural course of science, and not through judicial opinions.

- **BIOLOGICAL PLAUSIBILITY.** Drs. Leffler and Lebwohl do not get a pass on the requirement that their methodology be reliable just because "the biological mechanism to be considered need only be plausible, it does not need to be definite." Dkt. 1115 at 33. Plaintiffs do not dispute that the Marietta study central to Drs. Leffler and Lebwohl's mechanism opinions qualifies its findings on the need for "further study." Dkt. 1115 at 32. Nor do they dispute that the Scialom and Malamut papers did not aim to identify a mechanism of action, and expressly stated that the mechanism of action "remains to be elucidated." *Id.* at 33. Stretching studies beyond their reasonable limits is not a reliable basis upon which to form an expert opinion. *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 989-90 (8th Cir. 2001) (excluding expert opinion inappropriately extrapolated from case studies, medical texts, and other sources, where such studies did not explicitly support the opinion).

Drs. Leffler and Lebwohl's mechanism opinion is held together only by their *ipse dixit*, and plaintiffs acknowledge as much. Neither Dr. Leffler nor Dr. Lebwohl know how olmesartan causes what they term "olmesartan enteropathy." *See, e.g.,* Carroll Cert. Exhibit FF, Lebwohl Dep. at 71:12-73:22 ("I don't think we know enough to be sure yes or no" how olmesartan purportedly causes enteropathy); Leffler and Lebwohl Cert. Exhibit E, Lebwohl Rep. at 19 ("the immune response to this medication" is "as-yet fully characterized"). But they guess anyway, attempting to forge an analogy between "olmesartan enteropathy" and celiac disease. The fact that "olmesartan enteropathy is commonly compared to celiac disease in peer-reviewed literature" (Dkt. 1115 at 33; *accord* Dkt. 1109 at 16 (analogy is "a peer-reviewed fact")) does not make the analogy appropriate in the mechanism context. And Drs. Leffler and Lebwohl's expertise in the area of celiac disease does not justify unsupported leaps. *See, e.g., United States v. Mamah*, 332 F.3d 475, 478 (7th Cir. 2003) ("The court is not obligated to admit testimony just because it is given by an expert").

As noted in Defendants' opening brief, Drs. Leffler and Lebwohl claim that IL-15 expression – as seen in olmesartan patients in the Marietta paper – causes a destructive T-cell response resulting in enteropathy such as is seen in celiac patients. Dkt. 1066-1 at 32-33. The celiac literature these experts cite found this response with the expression of IL-15 in *both* the epithelium and lamina propria,

not just in the epithelium as was seen with olmesartan in the Marietta study. *See id.* According to plaintiffs, this distinction is of no concern, because Drs. Leffler and Lebwohl say so. Dkt. 1109 at 15 (quoting Dr. Lebwohl: "I believe that the link between these symptoms and this clinical phenotype and olmesartan can be explained . . . just like the link between gluten and feeling ill has biological plausibility); Dkt. 1115 at 32 (quoting Dr. Leffler: "in celiac disease you see cases where IL-15 levels are increased only in the epithelium"). That is not reliable ground for expert opinion. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) ("nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert").

* * *

Claiming that an expert employed a generally accepted methodology does not render the expert's opinions reliable. Though Drs. Leffler and Lebwohl profess to employ the Bradford-Hill methodology for assessing general causation, neither has done so in a reliable manner. "*Daubert*'s requirement that the expert testify to scientific knowledge – conclusions supported by good grounds for each step in the analysis – means that *any* step that renders the analysis unreliable under the *Daubert factors renders the expert's testimony inadmissible.*" *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3d Cir. 1994) (emphasis in original). Drs.

Leffler and Lebwohl's opinions that olmesartan can cause sprue-like enteropathy do not meet this standard, and should be excluded accordingly.

II. DRS. LEFFLER AND LEBWOHL'S EFFORT TO UNDERMINE THE SCIENTIFIC METHOD SHOULD BE REJECTED.

As Defendants' expert Dr. Jerrold Turner testified, there are many ways to form a reliable scientific basis for the opinion that olmesartan can cause sprue-like enteropathy. *See* Carroll Cert. Exhibit GG, Turner Dep. at 216:6-17 (identifying randomized controlled trials, animal studies, and controlled dechallenge/rechallenge as bases for establishing a causal nexus); *accord* FJC, Reference Manual on Scientific Evidence at 723-24 (3d ed. 2011) (describing the hierarchy of medical evidence). Drs. Leffler and Lebwohl, however, are unimpeded by the limitations in the existing science, and instead push headlong into a general causation opinion substantially on the back of unreliable case reports, case series, and adverse event reports. *See* Dkt. 1066-1 at 34-40. The Court should not endorse opinions predicated on unreliable sources simply because those sources are the most apt support for the opinions proffered. *See Daubert*, 509 U.S. at 590 ("Proposed testimony must be supported by appropriate validation – *i.e.*, 'good grounds,' based on what is known").

- ***First***, the hierarchy of scientific evidence should not be inverted because "randomized clinical trials" are "hardly relevant when specifically evaluating long-term, uncommon adverse events." Dkt. 1109 at 9. Even if that

were true (and the ROADMAP experience suggests otherwise (*see* Dkt. 1066-1 at 17-20)), a randomized clinical trial is not the only reliable way to establish causation. Plaintiffs would rather forge ahead instead of awaiting reliable evidence of "olmesartan enteropathy." That is not the stuff of admissible expert opinion. *See, e.g., Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996) ("Law lags science; it does not lead it").

Indeed, data from more reliable sources such as epidemiological publications exists, but Drs. Leffler and Lebwohl reject that data as coming from "underpowered" studies. *See* Dkt. 1109 at 6-8, 12-15 (supporting Dr. Lebwohl's discounting of epidemiological data contrary to his opinions); Dkt. 1115 at 19-28 (same, Dr. Leffler). Whatever the power of those studies, at least they were controlled and scientific. Case reports, case series, and adverse event reports are neither. *See, e.g., Ervin v. Johnson & Johnson, Inc.*, No. 2:04-cv-0205, 2006 WL 1529582, at *6 (S.D. Ind. May 30, 2006), *aff'd* 492 F.3d 901 (7th Cir. 2007), Leffler and Lebwohl Cert. Exhibit BB; *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1361-62 (N.D. Ga. 2001).

- ***Second,*** that certain case reports and adverse event reports refer to reported events that may be construed as "dechallenge" and "rechallenge" evidence does not justify abandoning the hierarchy of scientific evidence. *See* Dkt. 1109 at 10; Dkt. 1115 at 35-38. An unreliable source does not become reliable just

because the content supports plaintiffs' experts' opinions, however. Case reports and adverse event reports are still "[u]ncontrolled anecdotal information that offers one of the least reliable sources to justify opinions about both general and individual causation." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1250 (11th Cir. 2005); *accord* Carroll Cert. Exhibit FF, Lebwohl Dep. at 327:10-12 ("in every MedWatch report you're never going to get the entire story"). And none of the case reports and adverse event reports on which Drs. Leffler and Lebwohl rely present evidence of any controlled dechallenges or rechallenges of the sort that courts find akin to "controlled studies" (Dkt. 1115 at 36). *See, e.g.,* Carroll Cert. Exhibit GG, Turner Dep. at 74:13-16 (noting the absence of controlled data in case reports).

- ***Third***, plaintiffs cannot escape the methodological flaws of Dr. Leffler's reanalysis of MedWatch forms produced by Daiichi Sankyo (Dkt. 1115 at 38-39). Though plaintiffs acknowledge that Dr. David Kessler selected the forms for Dr. Leffler to review (Dkt. 1115 at 38), they ignore that his selection methodology is not reproducible and relies on Dr. Kessler's inexpert clinical assessment. Dkt. 1066-1 at 38-39 (describing the flaws in Dr. Kessler's selection methods). Further, though plaintiffs claim that Dr. Leffler applied the Naranjo criteria to the selected MedWatch reports (Dkt. 1115 at 39), they ignore that he applied that criteria in an inexpert manner. In particular, where a MedWatch report

did not include information concerning potential alternative causes – the sort of gap in information that courts have acknowledged makes adverse event reports unreliable – Dr. Leffler simply concluded that no alterative causes were at play, resulting in a skewed result suggesting a stronger signal for a causal nexus than is supported in the data. Dr. Leffler's flawed reanalysis of MedWatch reports should be excluded.

Drs. Leffler and Lebwohl's willingness to upend the hierarchy of scientific evidence to support their opinions demonstrates a lack of scientific rigor. Plaintiffs contend that because Drs. Leffler and Lebwohl have experience studying olmesartan outside the context of litigation, their opinions are more reliable. *See* Dkt. 1109 at 18; Dkt. 1115 at 16-17. But it's one thing for opinions in litigation to grow naturally from an expert's research (*Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 594 (D.N.J. 2002)), and another for an expert to carry preconceived conclusions into litigation and support them with data that courts have consistently held unreliable. Here, that is precisely what Drs. Leffler and Lebwohl have done, and this Court should not reward that effort. *Claar v. Burlington N. R.R. Co.*, 29 F.3d 499, 502-03 (9th Cir. 1994) ("Coming to a firm conclusion first and then doing research to support it is the antithesis of [the scientific] method").

Plaintiffs' citation to recent *Daubert* rulings in the *In Re Xarelto* litigation is

unavailing. The issues in that litigation and the specific challenges to the experts are not even remotely similar. Indeed, while plaintiffs rely on the Xarelto decision related to a plaintiff's expert, Dr. Winstead, it is worth noting that Dr. Winstead was not called to testify at trial, perhaps because the single opinion that was the subject of the *Daubert* challenge was repudiated by one of the plaintiffs' treating physicians. Unlike the ruling as to Dr. Winstead, Defendants challenge not just a single particular opinion, but the opinions of Drs. Lebwohl and Leffer in their entirety.

CONCLUSION

For the reasons set forth above and in the memorandum supporting their motion, Defendants respectfully request that the Court grant their Motion to Exclude Testimony of Dr. Daniel Leffler and Dr. Benjamin Lebwohl (Dkt. 1066).

Respectfully submitted,

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Dated: May 1, 2017